UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/535,312 | 06/05/2006 | Sung Youb Jung | 430156.404USPC | 5682 |

500 7590 08/27/2008

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104

| EXAMINER | |
|---|---|
| BRISTOL, LYNN ANNE | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1643 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/27/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/535,312 | JUNG ET AL. | |
| | Examiner | Art Unit | |
| | LYNN BRISTOL | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9 and 11-16* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11, 12, 14 and 16* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/14/08* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Claims 1-9 and 11-16 are all the pending claims for this application.

2. Claim 10 was cancelled, Claim 1, 6 12 and 13 were amended and new Claim 16 was added in the Response of 5/14/08.

3. Claim 15 is withdrawn from examination.

4. Claims 1-9, 11-14 and 16 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This action is FINAL.

***Withdrawal of Objections***

***Oath/Declaration***

6. The objection to the Oath/Declaration for failing to identify the mailing address of each inventor and the city and either state or foreign country of residence of each inventor is withdrawn in view of Applicants comments on p. 8 of the Response of 5/14/08. (MPEP 601.03).

***Specification***

7. The objections to the specification are withdrawn for the following reasons:

a) The specification has been amended to cross-reference the priority documents for this application.

b) The legends to Figures 1-3 and 5 on p. 9 of the specification have been amended to provide sufficient description for each of the figures.

***Withdrawal of Rejections***

***Claim Rejections - 35 USC § 112, second paragraph***

8. The rejection of Claims 1-10, 12 and 14 for the recitation "E. coli-derived signal sequence" in Claims 1 and 10 is moot for cancelled Claim 10 and withdrawn for Claims 1-9, 12 and 14 in view of the amendment of the claims to recite "a signal sequence isolated from E. coli."

9. The rejection of Claims 2-5 for the recitation "and combinations and hybrids thereof" in Claims 2 and 3 for any one of the IgG, IgA, IgM, IgE or IgD isotypes is withdrawn based on Applicants allegations in the middle of p. 10 of the Response of 5/14/08.

10. The rejection of Claims 6 and 7 for the recitation "the immunoglobulin region is composed of one to four domains selected from the groups consisting of CH1, CH2, CH3, CH4 and CL domains" in Claim 6 is withdrawn in view of the amendment of the claim to delete the limitation for "CL" domain.

11. The rejection of Claim 12 for the recitation "pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K" because the expression vectors are referred to by a laboratory designation is withdrawn in view of the deletion of the phrase from the claim.

***Claim Rejections - 35 USC § 112, first paragraph***

***Biological Deposit (1)***

12. The rejection of Claim 12 under 35 U.S.C. 112, first paragraph, as failing to enable one skilled make and/or use the expression vectors is withdrawn.

Applicants have amended Claim 12 to delete the expression vectors pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, and pSTIIG4H_K.

***Biological Deposit (2)***

13. The rejection of Claim 13 under 35 U.S.C. 112, first paragraph, as failing to enable one skilled in the art to make the E. coli transformants for HMI0927, HMI0928, HMI0929, HMI0930, HMI0931, HMI0932, HMI0933, HMI0934, HMI0935, or HMI0936 is withdrawn.

Applicants' allegations in ¶2 on p. 12 of the Response of 5/14/08 and the amendment of the claim overcome the rejection.

Copies of deposit receipts for the E. coli transformants, HMI0927, HMI0928, HMI0929, HMI0930, HMI0931, HMI0932, HMI0933, HMI0934, and HMI0935, are provided at the end of the specification filed 5/17/05. The claim has been amended to recite the deposit numbers.

The E. coli transformant HMI0936 has been deleted from the claim.

Applicants' statement of assurances appears in ¶2 on p. 12 of the Response of 6/6/08.

***Claim Rejections - 35 USC § 102***

14. The rejection of Claims 1, 2, 6, 8, 10 and 14 under 35 U.S.C. 102(b) as being anticipated by Adib-Conquy et al. (Protein Engineering 8:859-863 (1995); cited in the PTO 892 form of 8/7/07) is withdrawn in view of the amendment of Claim 1 to recite "the signal sequence is a heat-stable enterotoxin signal sequence."

15. The rejection of Claims 1-4, 6-8 and 14 under 35 U.S.C. 102(e) as being anticipated by Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) is withdrawn in view of the amendment of Claim 1 to recite "the signal sequence is a heat-stable enterotoxin signal sequence."

16. The rejection of Claims 1-8, 10 and 14 under 35 U.S.C. 103(a) as being unpatentable over Cox et al. (WO 01/03737; published 1/19/01) in view of Adib-Conquy et al. (Protein Engineering 8:859-863 (1995); cited in the PTO 892 form of 8/7/07) is withdrawn in view of the amendment of Claim 1 to recite "the signal sequence is a heat-stable enterotoxin signal sequence."

17. The rejection of Claims 1 and 9 under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Sun et al. (USPN 6797493; published 9/28/04; filed 10/1/01) is withdrawn in view of the amendment of Claim 1 to recite "the signal sequence is a heat-stable enterotoxin signal sequence."

***Rejections Maintained***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Enablement***

18. The rejection of Claims 2-7 (and now Claim 8) under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for Ig constant regions that are combinations and hybrids of IgG, IgA, IgM, IgE, IgD or IgG1, IgG2, IgG3, IgG4 or CH1, CH2, CH3, CH4 and CL is maintained.

Claim 8 has been joined under the rejection because it is drawn to a heavy chain constant region and a light chain constant region and encompasses any Ig constant region and any light chain where Applicants admit on the record (and by amendment of Claim 6 and addition of new Claim 28) that the nucleotide sequence would comprise a CL domain or any one to four domains CH1, CH2, CH3 and CH4 but not the combination. Claim 8 reads on the combination or a nucleotide comprising any CL and any heavy chain region.

The rejection was set forth in the previous Office Action as follows:

> "Nature of the Invention/Skill in the Art
> Claims 2-7 are interpreted as being drawn to a method of producing an Ig constant region comprising transforming a prokaryotic cell with an expression vector including an E. coli derived signal sequence and a nucleotide sequence encoding an Ig constant region, culturing the transformant and isolating and purifying the Ig constant region where the Ig constant region is IgG, IgA, IgM, IgE, IgD and combinations and hybrids thereof (Claim 2), or IgG1, IgG2, IgG3, IgG4 and combinations and hybrids thereof (Claim 3), or the Ig constant region is an IgG4 constant region (Claim 4) or the Ig constant region is a human aglycosylated IgG4 constant region (Claim 5), or the Ig constant region is one to four domains of CH1, CH2, CH3, CH4 or CL (Claim 6), and the Ig constant region of Claim 6 further comprises a hinge region (Claim 7).

The relative skill in the art required to practice the invention is a molecular immunologist with a background in molecular biology and antibody chemistry.

Disclosure in the Specification

The specification does not provide a sufficient enabling description of the claimed invention. The disclosure appears to show only antibodies with certain specified amino acid substitutions. For example, the specification discloses expression vectors encoding engineered Ig constant domains such as pSTIIgICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIgIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K. The instant claims encompass in their breadth any vector encoding any "combinations and hybrids" of a constant region from IgG, IgA, IgM, IgE, or IgD, or of a constant region of IgG1, IgG2, IgG3, IgG4, or of one to four domains of CH1, CH2, CH3, CH4 or CL.

Prior Art Status: Fc modifications

There does not appear to be sufficient guidance in the specification as field as to how the skilled artisan would make and use the claimed "combinations and hybrids thereof" or the "one to four domains…CH1, CH2, CH3, CH4 and CL." The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies. For example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969) show that even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968). Further, Lazar et al. (WO 03/074679) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an Fc region of an antibody may cause a loss in affinity for its antigen (see entire document, particularly page 3).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict such "combinations and hybrids thereof" and the combination of which "one to four domains of… CH1, CH2, CH3, CH4 and CL" have the same function as the instant claimed invention. Reasonable correlation must exist between the scope of the claims and scope to enablement set forth. Applicant does not appear to provide guidance as to other "combinations and hybrids thereof" or which if any combination of "one to four domains of… CH1, CH2, CH3, CH4 and CL" can be combined, and that meet all of the claimed limitations.

The specification does not appear to provide sufficient guidance as to which constant domains should or should not be changed to preserve any particular function. The variation permitted by the instant claim language is extensive. There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed such "combinations and hybrids thereof" and the combination of which "one to four domains of… CH1, CH2, CH3, CH4 and CL." The specification provides no direction or guidance regarding how to produce such "combinations and hybrids thereof" and the combination of "one to four domains of… CH1, CH2, CH3, CH4 and CL" as broadly defined by the claims. In view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention."

Applicants allegations on pp. 12-13 of the Response of 5/14/08 and their admissions of record on the bottom of p. 10 of the Response have been considered and are not found persuasive.

Applicants allege that in amending Claim 6 to recite the Ig constant region is composed of one to four domains selected from CH1, CH2, CH3 and CH4 domains overcomes the rejection for this claim; the method is directed to mass expression and purification of Ig constant regions using a heat-stable enterotoxin II signal sequence "*regardless of immunoglobulin function*"; Example 3 shows how to produce dimeric and

monomeric Ig constant region constructs; and Example 4 teaches how to express and purify the constructs.

Response to Arguments

Initially, the examiner submits that Applicants are erroneous in asserting or advancing the position- that they are not required to demonstrate the production of a functional Ig constant region by the claimed method steps. This is contrary to the statutory requirement under 112, first paragraph, for an enabling use of the method. One of skill in the art would not be enabled to use the immunoglobulin constant regions produced by the method if the embodiments are inoperative. As noted in *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971), if "compositions are in fact useless, appellant's specification cannot have taught how to use them." 439 F.2d at 1243, 169 USPQ at 434."

MPEP 2161 "An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975) ("[A] specification which describes' does not necessarily also enable' one skilled in the art to make or use the claimed invention.")."

MPEP 2164.01(b) "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27USPQ2d 1510, 1513 (Fed. Cir. 1993)."

Secondly, Examples 3 and 4 in the specification show how to produce and express a full length IgG4 heavy chain constant region (CH1-hinge-CH2-CH3) under the control of one promoter and a full length light chain constant region (CL) under the control of a separate promoter. The heavy and light chain are taught as forming a dimer or tetramer linked thru free cysteine residues in each chain. Thus the specification is not enabling for producing constructs comprising a) a heavy chain region that comprises a CH1, hinge, CH2, CH3 (or CH4) domains from any combination of different Ig molecules or b) expressing a hybrid heavy chain with any CL chain to form a dimer because cysteine cross-linking is required for dimerization.

Thirdly, Applicants have not addressed the art references cited in the original rejection which teach and recognize that changes in function(s) are predictable by introducing even minor changes to the Fc domains.

The rejection is maintained because Applicants' attorney arguments do not take the place of supplemental evidence showing an enabling use for the full scope of the method claims and the Ig constant regions produced thereby (Arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection (MPEP 2144.03)).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Reilly et al. (US20050048572; published March 3, 2005; filed 10/30/03) is maintained.

The rejection was set forth in the previous Office Action as follows:

"The interpretation of Claims 1 and 10 is discussed supra. Claim 10 is further drawn to where the signal peptide is penicillinase, lpp, heat-stable enterotoxin II, LamB, PhoE, PelB, and OmpA, and Claim 11 is drawn to the heat stable enterotoxin signal peptide of SEQ ID NO: 36.

The method claims for producing an Ig constant region from a prokaryotic cell transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide was prima facie obvious at the time of the invention over Capon and Reilly.

The interpretation of Capon is discussed supra [under

Reilly discloses methods of expressing Fc fusion proteins from expression plasmids encoding Fc portions of heavy and light chains from transformed E. coli [0285], where the a recombinant vector comprises a secretion signal sequence component for prokaryotic host cells that do not recognize and process the signal sequences native to the heterologous polypeptides, and the signal sequence is substituted by a prokaryotic signal sequence such as alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP. Reilly teaches that the signal sequences used in both cistrons of the expression system are STII signal sequences or variants thereof [0122]. Reilly teaches using "the heat-stable enterotoxin II signal sequence (STII) (Picken et al.,

Infect. Immun. 42:269-275, 1983, and Lee et al., Infect. Immun. 42:264-268, 1983) for the periplasmic secretion of heavy and light chains, and fine control of translation for both chains was achieved with previously described STII signal sequence variants of measured relative translational strengths, which contain silent codon changes in the translation initiation region (TIR) (Simmons and Yansura, Nature Biotechnol. 14:629-634, 1996; Simmons et al., J. Immunol. Methods (2002) 263:133-147)" [0216]. Applicants specification teaches that the native heat-stable enterotoxin (STII) has the sequence of SEQ ID NO:36 (p. 18, lines 8-11), thus by incorporation through reference to Simmons and Yansura (see Table 1, WT SII nucleotide sequence), Reilly teaches the wt heat-stable enterotoxin signal peptide corresponding to SEQ ID NO: 36.

One skilled in the art at the time of the invention would have been motivated to have produced and been reasonably assured of success in having produced the method invention based on the combined disclosure of Capon and Reilly. Both Capon and Reilly expressly teach methods using transformed prokaryotic cells to express an Ig constant region where the transformant is transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide and culturing the cells to express for purification the Ig constant region. Both Capon and Reilly expressly teach bacterial signal sequences, where Reilly more specifically teaches using the E. coli-derived signal sequences alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP, and more specifically, the wt heat-stable enterotoxin signal peptide of SEQ ID NO:36. Because each of the references appreciates and teaches signal peptides as being critical to the respective host and bacterial signal peptides had been shown by both references to enable the expression of heavy and light chain constant regions in transformed E. coli, one skilled in the art would have found more than sufficient motivation and been reasonably assured of success in having introduced the E. coli-derived signal peptide sequences of Reilly into the method of Capon in order to arrive at the objective of the instant claimed method. For all of the foregoing reasons, the method was prima facie obvious over Capon and Reilly."

Applicants' allegations on p. 18 of the Response of 5/14/08 have been considered and are not found persuasive. Applicants allege "Applicants describe the surprising and unexpected results of an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form; a protein expression strategy that is much more effective than conventional methods based on secreting proteins into the periplasmic space (see as-filed specification, page 26, line 25 to page 28, line 13). Furthermore, Applicants provide experimental evidence supporting the surprising and unexpected cytoplasmic, water-soluble immunoglobulin constant region protein expression (see, e.g., Example 4 and Figure 1)."

Response to Arguments

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies

(i.e., an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

20. The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Reilly et al. (US20050048572; published March 3, 2005; filed 10/30/03) as applied to claims 1 and 10 above, and further in view of Kwon et al. (USPN 6605697; published 8/12/03; filed 6/14/01) is maintained.

The rejection was set forth in the previous Office Action as follows:

"The interpretation of Claims 1 and 10 is discussed supra. Claim 11 is drawn to the heat stable enterotoxin signal peptide of SEQ ID NOS: 36-46.

The method claims for producing an Ig constant region from a prokaryotic cell transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide comprising a heat-stable enterotoxin signal peptide was prima facie obvious at the time of the invention over Capon and Reilly in view of Kwon.

The interpretation of Capon and Reilly is discussed supra.

Kwon discloses expression of fusion proteins in prokaryotic cells where the fusion protein is encoded by a sequence comprising a bacterial-derived signal peptide, and more especially the heat stable enterotoxin peptides (STII) corresponding to SEQ ID NOS:36-46 of Claim 11 are disclosed. See SEQ ID NOS: 1 and 13-22 of Kwon (Table 2). Kwon teaches that the yield of secreted heterologous protein decreases as the secretory efficiency of the signal peptide becomes low. Therefore, the yield of secreted heterologous proteins may be enhanced by modifying the signal peptide moiety of fusion proteins expressed in host microorganisms.

One skilled in the art at the time of the invention would have been motivated to have produced and been reasonably assured of success in having produced the method invention based on the combined disclosure of Capon, Reilly and Kwon. Both Capon and Reilly expressly teach methods using transformed prokaryotic cells to express an Ig constant region where the transformant is transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide and culturing the cells to express for purification the Ig constant region. Both Capon and Reilly expressly teach bacterial signal sequences, where Reilly more specifically teaches using the E. coli-derived signal sequences alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP, and more specifically, the wt heat-stable enterotoxin signal peptide of SEQ ID NO:36. Kwon alos teaches using the signal sequence of SEQ ID NO:36 for the wild type heat stable enterotoxin II signal peptide and variants thereof in order to express heterologous fusion proteins in E. coli expression systems. Further because Kwon appreciates the sensitivity of the signal peptide sequence in achieving the stability, e.g., expression of the full length fusion protein in a prokaryotic system and provides examples that are shown to work using various fusion proteins, one skilled in the art would have found more than sufficient motivation to have introduced the heat stable enterotoxin signal peptides of Reilly and Kwon into the method of Capon and Reilly in order to reliably and reproducibly express an Ig constant region from a prokaryotic system. Because each of the

references appreciates and teaches bacterial signal peptides as being critical to the respective host, and bacterial signal peptides had been shown by all of the references to enable the expression of fusion proteins, where Capon and Reilly further demonstrate expression of heavy and light chain constant regions in transformed E. coli, one skilled in the art would have found more than sufficient motivation and been reasonably assured of success in having introduced the E. coli-derived signal peptide sequences of Reilly and kwon into the method of Capon in order to arrive at the objective of the instant claimed method. For all of the foregoing reasons, the method was prima facie obvious over Capon and Reilly and Kwon."

Applicants' allegations on p. 19 of the Response of 5/14/08 have been considered and are not found persuasive. Applicants allege neither of the three references describe the surprising and unexpected results of an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form; a protein expression strategy that is much more effective than conventional methods based on secreting proteins into the periplasmic space.

Response to Arguments

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

## ***New Grounds for Objection***

### ***Drawings***

21. In addition to Replacement Sheets containing the corrected drawing figure(s) for Figure 4, applicant is required to submit a marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version. The marked-up copy must be clearly labeled as "Annotated Sheets" and must be presented in the amendment or remarks section that explains the change(s) to the drawings. See 37 CFR 1.121(d)(1). Failure to timely submit the proposed drawing and marked-up copy will result in the abandonment of the application.

### ***Claim Objections***

22. Claim 11 is objected to for depending from cancelled Claim 10. Appropriate correction is required.

## ***New Grounds for Rejection***

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claims 1-9, 11, 12, 14 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the method in an E. coli bacterium using the E. coli signal sequence for heat-stable enterotoxin II fused to an

immunoglobulin constant region for expressing a water-soluble protein in the cell cytoplasm where the E. coli transformant is E. coli BL21/pSTIIGICHI_3(HM10935), BL21/pSTIIdCG 1 Fc (HM10927), BL21/pSTIIdCG 1SFc (HM 10928), BL21/pSTIIdCG 1SFFc (HM 10929), BL21/pSTIIG1Mo (HM10930), B L21/pSTIIdCG4Fc (HM 10932), BL21/pSTIIGICH 1_3 (HM 10931), BL21/pSTIIG4Mo (HM10933), and BL21/pSTIIG4H_K (HM 10934), does not reasonably provide enablement for practicing the method in any prokaryotic cell transfected with any expression vector encoding the E-coli heat-stable enterotoxin II signal sequence fused to any immunoglobulin constant domain in order to obtain a water soluble protein localized in the bacterial cell cytoplasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 1-9, 11, 12, 14 and 16 are interpreted as being broadly drawn to producing an immunoglobulin constant region from any transformed prokaryotic cell with

any recombinant expression vector comprising any nucleotide sequence encoding any signal sequence for an E. coli heat-stable enterotoxin II signal sequence and encoding any immunoglobulin constant region, and culturing the transformant in order to isolate and purify the expressed immunoglobulin constant region.

The relative skill in the art required to practice the method is a molecular biologist/ molecular immunologist.

Disclosure in the Specification

The specification teaches that in order to mass produce an Fc domain in E. coli cells,one should use an E. coli signal sequence, and preferably containing an E. coli heat-stable enterotoxin II signal sequence. A vector, which includes an enterotoxin II Shine-Dalgarno (SD) sequence along with an enterotoxin II signal sequence, is more preferable because it further enhances expression levels of a target protein. In the present invention, to express an enterotoxin II signal sequence-immunoglobulin heavy chain region fusion protein, a nucleotide sequence encoding an enterotoxin II Shine-Dalgarno (SD) sequence and an enterotoxin II signal sequence is linked to another nucleotide sequence encoding an immunoglobulin heavy chain region by a genetic recombination method in such a way as to be expressed in frame under the control of a promoter (p. 21); the following recombinant expression vectors: pSTIIG1CH1.sub.--3 expressing an immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 25; pSTIIdCG1Fc expressing an immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 21; pSTIIdCG1SFc expressing an

immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 22; pSTIIdCG1SFFc expressing an immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 23; pSTIIG1Mo expressing an immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 27; pSTIIdCG2Fc expressing an immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 35; pSTIIdCG4Fc expressing an immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 29; pSTIIG4CH1.sub.--3 expressing an immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 24; and pSTIIG4Mo expressing an immunoglobulin heavy chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 30 (pp. 21-22); and a recombinant expression vector, pSTIIG4H_K, expresses an immunoglobulin heavy chain constant region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 24, and an immunoglobulin light chain region including an enterotoxin II signal sequence and the amino acid sequence of SEQ ID NO. 34, under the control of independent promoters (pp. 22-23); and the recombinant expression vectors are individually introduced into E. coli, thus generating the following transformants: BL21/pSTIIG1CH1.sub.--3(HM10935) transformed with pSTIIG1CH1.sub.--3; BL21/pSTIIdCG1Fc (HM10927) transformed with pSTIIdCG1Fc; BL21/pSTIIdCG1SFc (HM10928) transformed with pSTIIdCG1SFc;

BL21/pSTIIdCG1SFFc (HM10929) transformed with pSTIIdCG1SFFc; BL21/pSTIIG1Mo (HM10930) transformed with pSTIIG1Mo; BL21/pSTIIdCG2Fc (HM10936) transformed with pSTIIdCG2Fc; BL21/pSTIIdCG4Fc(HM10932) transformed with pSTIIdCG4Fc; BL21/pSTIIG4CH1.sub.--3(HM10931) transformed with pSTIIG4CH1.sub.--3; BL21/pSTIIG4Mo(HM10933) transformed with pSTIIG4Mo; and BL21/pSTIIG4H_K(HM10934) transformed with pSTIIG4H_K (pp. 24-25).

The specification does not teach, suggest or demonstrate that the E. coli signal sequence for entertoxin II could be expressed and would be functional in any other prokaryotic cell other than an E. coli bacterium. The specification is not enabling for using any expression vector encoding the E. coli signal sequence and an immunoglobulin constant region in just any transformed prokaryotic cell (e.g., a bacterium other than E. coli) in order to isolate and purify the expressed protein. The ordinary artisan would be required to perform undue experimentation in preparing the expression vector encoding the E-coli signal sequence and to have the fused immunoglobulin constant region protein expressed in just any other bacterium.

***Conclusion***

24. No claims are allowed.

25. Claim 13 is objected to as depending from a rejected base claim.

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643